PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 9/00, 31/465

A1

(11) International Publication Number: WO 93/12764

(43) International Publication Date: 8 July 1993 (08.07.93)

(21) International Application Number: PCT/CA93/00003

(22) International Filing Date: 4 January 1993 (04.01.93)

(30) Priority data:
9200047.0 3 January 1992 (03.01.92) GB

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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITION TO HELP STOP SMOKING

(57) Abstract

A nicotine-containing composition for nasal administration is provided to assist in reduction of the desire of a subject to smoke tobacco or to provide a substitute for tobacco smoking.

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COMPOSITION TO HELP STOP SMOKING.

This invention relates to compositions and methods useful for subjects who wish to reduce tobacco smoking or to find a socially acceptable substitute.

Background of the Invention

Because of the reported harmful effects of tobacco smoking and also due to the current social attitudes to smoking, resulting in ever-increasing smoke-free public areas, there is great pressure on tobacco smokers to stop smoking or to find a more socially acceptable alternative.

For those who are unable to give up smoking completely, various forms of nicotine-replacement therapy have been suggested.

Nicotine-containing chewing gum is available commercially and has provided a satisfactory substitute for tobacco-smoking for some people. For many people, nicotine gum does not alleviate the craving for tobacco, due to the gradually achieved and low blood nicotine levels produced. Many people also experience unpleasant side effects, such as nausea and indigestion (Jarvis et al., British Medical Journal, Vol. 285, p. 537 (1982); Schneider, Comprehensive Therapy, Vol. 13, p. 32 (1987)).

Nicotine-containing nose drops have been reported (Russell et al., British Medical Journal, Vol. 286, p. 683 (1983); Jarvis et al., Brit. J. of Addiction, Vol. 82, p. 983 (1987)). Nose drops, however, are difficult to administer and are not convenient for use at work or in other public situations. There may also be local nasal irritation with use of nicotine nose drops. The difficulty in administration also results in unpredictability of the dose of nicotine administered.

The use of skin patches for transdermal administration of nicotine has been reported (Rose, in Pharmacologic Treatment f Tobacco Dependence, (1986) pp.

158-166, Harvard Univ. Press). Nicotine-containing skin patches can cause local irritation and the absorption of nicotine is slow and affected by cutaneous blood flow.

U.S. Patents Nos. 4,920,989 and 4,953,572 disclose the use of an inhaled nicotine aerosol, sometimes in conjunction with nicotine skin patches, as a means of reducing tobacco smoking. When skin patches were used, transdermal absorption of nicotine gave blood nicotine levels comparable to those achieved by tobacco smoking. The use of the nicotine aerosol alone delivered substantially less nicotine to the blood than is seen while smoking tobacco but did provide sensations of irritation in the airways of the user, thus mimicking sensations associated with tobacco smoking.

In order to ensure that the droplets of nicotine solution would be carried into the respiratory airways on inhalation through the mouth in imitation of smoking, rather than being deposited in the oral cavity, the aerosol droplet size employed was 10 microns or less.

Although a certain degree of airway irritation is desired to mimic smoking, this cannot be readily controlled and the irritation may be pronounced, making the use of a nicotine aerosol undesirable.

Perkins et al. (Behavior. Research Methods, Instruments and Computers (1986), vol. 18, p.420 and Psychopharm. (1989), vol. 97, p. 529) reported use of a nicotine aerosol spray as a means of administering nicotine to a test subject in controllable amounts in order to study the physiological effects of nicotine. Under their test conditions, they were able to employ a dilute solution of nicotine administered in several doses to deliver 1.8 ml. over a 5 minute period to resting subjects and did not investigate a practical nicotine preparation for everyday use, such as is required for anti-smoking treatm nt or as a substitute for tobacco smoking.

U.S. Patent No. 4579858 discloses a nicotine-containing preparation of high viscosity which is administered to the nose as a viscous plug. The surface area of such a plug which is in contact with the nasal mucosa is limited and this is reflected in the relatively low blood nicotine levels achieved by this method of nicotine administration.

There remains a need for a nicotine preparation suitable as a substitute for tobacco smoking, which can be conveniently used in public, as the subject goes about his or her normal activities over an extended period of time.

Summary of Invention

A composition for nasal administration is provided to assist in reduction of the desire of a subject to smoke tobacco or to provide a substitute for tobacco smoking, the composition comprising a solution of nicotine or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable solvent, the composition having a pH in the range of about 5 to about 6.5, a nicotine concentration in the range of about 10 to about 40 mg/ml and containing a suitable agent to produce a viscosity in the range of about 1 to about 99 centipoise.

Summary of the Drawings

The invention, as exemplified by preferred embodiments, is described with reference to the drawings in which:

Figure 1 shows the blood nicotine level of a subject at various time intervals after administration of the nicotine-containing composition of the invention.

Detailed Description of the Invention

The present invention provides a convenient, inexpensive and effective alternative to tobacco smoking,

by administration of an effective dose of nicotine by nasal spray to a subject.

Nicotine-containing compositions and nasal sprays suitable for nasal administration are also provided.

The smoking alternative provided by the present invention may be used to assist those attempting to stop tobacco smoking or may be used indefinitely as a substitute for tobacco smoking which avoids both the undesired side effects of tobacco smoking on other people in the vicinity of the smoker and also the deleterious effects on the smoker of other substances such as carcinogens and carbon monoxide in tobacco smoke. The nicotine-containing compositions and sprays of the invention may be used without interference with the user's productive work or other normal activities.

When a nicotine-containing solution is applied to the nasal mucosa, nicotine can be absorbed directly into the bloodstream. If a smoking substitute is to be provided by this means, sufficient nicotine must be applied and absorbed to give a rapid increase in blood nicotine comparable to that achieved by tobacco smoking if the craving to smoke is to be eliminated. Previously available smoking substitutes often fail in this regard due to a too small or too delayed increase in blood nicotine level.

It is desirable that nasal administration of nicotine provides a sufficient dose of nicotine to a sufficiently large area of the nasal mucosa to give the desired rapid increase in blood nicotine level without providing a local nicotine concentration so high that it causes mucosal irritation and without requiring the delivery of such a large volume of nicotine-containing composition that a portion of the administered dose runs from the nose, causing annoyance and inconvenience to the user.

In accordance with the present invention, nicotine or a pharmaceutically acceptable nicotine salt is

dissolved in a pharmaceutically acceptable solvent, such as phosphate-buffered saline, and is adjusted to a pH in the range of about 5 to about 6.5, for optimal absorption through the nasal mucosa. A pH of about 5.8 is preferred.

Pharmaceutically acceptable nicotine salts are known to those skilled in the art and include nicotine tartrate and nicotine hydrogen tartrate.

Other suitable pharmaceutically acceptable buffering agents will be known to those skilled in the art.

In order to improve retention of the nicotine-containing composition of the invention in the nose, a suitable agent is added to produce a viscosity in the range of about 1 to about 99 centipoise. A viscosity in the range of about 10 to about 20 centipoise is preferred.

As will be known to those skilled in the art, a variety of agents may be used to produce the desired viscosity, including cellulose, substituted celluloses such as carboxymethyl cellulose and methyl cellulose, gum arabic and polyethylene glycol. The desired viscosity may also be produced by use of an oil emulsion, the oil phase being any suitable nasally-acceptable oil including, for example, lanolin or beeswax. Any viscosity producing agent used must, of course, be pharmaceutically acceptable and well tolerated by the nasal mucosa.

The nicotine-containing composition of the present invention is applied to the nose as a spray of droplet size selected to favour deposition of the droplets in the nose and minimise inhalation of the nicotine composition into the airways beyond the nose.

Studies by Yu et al (J. Pharmaceut. Sci., Vol. 73, p. 344 (1984)) have shown that droplet size of a spray delivered into the nose or inhaled through the mouth influences the location of droplet deposition. These authors showed that, during inhalation, droplets of 2 to

6 microns largely reach the terminal bronchi and alveoli, whereas a majority of droplets greater than 10 microns is required to localise delivery in the nose.

The nicotine-containing composition of the invention may be applied to the nose by any suitable atomiser or spray device which produces a spray of droplet size greater than about 10 microns. For example, conventional venturi-type atomisers such as are used for nasal decongestants or metered dose spray devices such as are used for nasal steroid application may be employed. These devices produce 98% of droplets greater than 16 microns and a majority of droplets of approximately 100 to 200 microns. As will be understood by those skilled in the art, the viscosity of the composition of the invention should be optimised for the type of spray device employed. For example, it has been found by the inventors that when a venturi-type atomiser is used, the nicotine composition should have a viscosity of not more than about 10 centipoise. When a metered dose spray device is used, a composition of viscosity up to about 30 centipoise may be used with good droplet production, with increasing viscosities above that tending to produce a stream of liquid rather than an aerosol. A suitable composition viscosity for a particular type of spray device may be readily determined by those skilled in the art.

When the nasal spray of the invention is used, nicotine is not drawn into the user's airways beyond the nose, thus avoiding respiratory irritation and allowing the use of higher nicotine concentrations, permitting blood nicotine levels to be boosted to those comparable with smoking without concomitant irritation.

As will be understood by those skilled in the art, the nicotine concentration in the composition of the invention and the volume of composition delivered to the nose may be varied to provide a desired nicotine dose to a subject. The volume delivered should be selected to as

to be well retained in the nose, without running out. The nicotine concentration should not be so high as to produce unacceptable local irritation when sprayed in the required amount.

The inventors have found that the composition of the invention can be applied in a volume of about 0.03 to about 0.08 ml. per nostril with good retention of the composition in the nose. A nicotine concentration in the range of about 10 to about 40 mg/ml is well tolerated by the nasal mucosa when applied in accordance with the present invention.

In order to approximate the dose of nicotine delivered to the blood by smoking one cigarette, ie. approximately 1 mg (Russell et al., above), about 2 mg nicotine should be delivered to the nose. If, for example, an atomiser delivering about 0.03 ml. nicotine composition per squeeze is employed, and the composition has a concentration of 20 mg/ml nicotine, one squeeze delivers 0.06 mg nicotine and three applications will deliver approximately 2 mg nicotine.

In accordance with a preferred embodiment of the invention, a composition having a viscosity of about 10 centipoise and nicotine concentration about 20 mg/ml, dissolved in phosphate buffered saline at a pH of about 5.8 is employed. The composition is delivered to the nose by a spray device which delivers about 0.03 ml. of the composition per activation of the device in the form of a spray having droplets of at least 10 microns diameter.

The nicotine composition of the invention may also optionally contain one or more of a flavouring agent such as menthol, and a preserving agent such as benzoic acid or an antioxidant such as ascorbic acid. Suitable flavourings and preservatives acceptable in foods and pharmaceuticals will be known to thos skilled in the art, as will suitable concentrations of these agents.

Use of nicotine-containing compositions of the invention applied as a nasal spray in accordance with the invention has been found to be well tolerated by human subjects, with minimal side effects in the form of a mild and temporary runny nose.

Use of the nicotine-containing nasal spray of the invention has been found to permit a smoker to function efficiently in a non-smoking work environment for at least three years without withdrawal symptoms or tobacco cravings.

The following examples are merely illustrative of the invention and the invention is not necessarily limited thereto.

Example 1

Nicotine (98 - 100% free base, catalogue # 3876, Sigma Chemical Co., St Louis, Mo.) was dissolved in phosphate buffered saline (PBS: 0.175 g Na_2HPO_4/100 ml; 1.21 g NaH_2PO_4/100 ml; 0.292 g NaCl/100 ml) to give a nicotine concentration of 20 mg/ml. This solution has a pH of 5.8 and an osmolarity of 290 mOsm. Carboxymethyl-cellulose was added to give a viscosity of 5 centipoise. The solution was sterilised by passing it through a 0.2 micron filter and 10 ml of the sterilised solution was placed in a conventional venturi-type atomiser.

The atomiser was used to administer 2.4 mg nicotine to the nose of a human subject over about 5 seconds, by four squeezes of the atomiser (two squeezes into each nostril). Blood samples were collected from an anticubital vein in the arm of the subject at various time intervals after nicotine administration (time zero in Figure 1) and blood nicotine concentrations were determined by the method of Feyerabend and Russell (J. Pharm. Pharmacol., Vol. 32, pp. 178 - 181 (1980)). Results are shown in Figure 1.

The concentrations of blood nicotine achieved were similar to those resulting from smoking of a cigarette

and the peak value occurred around 15 minutes from administration, only slightly later than after cigarette smoking.

Although only preferred embodiments of the invention have been described and illustrated, the present invention is not limited to the features of these embodiments, but includes all variations and modifications within the scope of the claims.

I Claim:

1. A composition for nasal administration to assist in reduction of the desire of a subject to smoke tobacco or to provide a substitute for tobacco smoking, the composition comprising

a solution of nicotine or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable solvent, the composition having a pH in the range of about 5 to about 6.5, a nicotine concentration in the range of about 10 to about 40 mg/ml and containing a suitable agent to produce a viscosity in the range of about 1 to about 99 centipoise.

2. A composition in accordance with claim 1 wherein the pharmaceutically acceptable solvent is phosphate buffered saline.

3. A composition in accordance with claim 2 wherein the viscosity producing agent is cellulose or a substituted cellulose.

4. A composition in accordance with claim 3 wherein the viscosity producing agent is carboxymethyl cellulose.

5. A composition in accordance with claim 2 wherein the viscosity producing agent is a pharmaceutically acceptable oil emulsion.

6. A composition in accordance with claim 2 wherein the pH is about 5.8, the nicotine concentration is about 20 mg/ml and the composition contains carboxymethyl cellulose to produce a viscosity of about 5 to about 20 centipoise.

7. A nicotine-containing spray comprising the composition of any one of claims 1 to 6 in the form of droplets of a size range selected to favour deposition of the droplets in the nose.

8. A nicotine-containing spray comprising the composition of any one of claims 1 to 6 in the form of droplets of at least about 10 microns in diameter.

9. A nicotine containing spray comprising the composition of any one of claims 1 to 6 in the form of droplets of a size within the range of about 100 to about 200 microns in diameter.

10. A composition in accordance with any one of claims 1 to 6 wherein the composition is in a spray device suitable for delivering an effective dose of the composition to the nose in the form of droplets of a size range selected to favour deposition of the droplets in the nose.

11. A composition in accordance with any one of claims 1 to 6 wherein the composition is in a spray device suitable for delivering an effective dose of the composition to the nose in the form of droplets of at least about 10 microns in diameter.

12. A method of assisting in the reduction of the desire of a subject to smoke tobacco comprising administering an effective dose of a composition in accordance with any one of claims 1 to 6 to the nose of the subject.

13. A method of assisting in the reduction of the desire of a subject to smoke tobacco comprising administering a composition in accordance with any one of

claims 1 to 6 to the nose of the subject in an amount which delivers a nicotine dose in the range of about 1 to about 3 mg.

14. A method of assisting in the reduction of the desire of a subject to smoke tobacco comprising administering an effective dose of a nicotine-containing spray in accordance with any one of claims 7 to 8 to the nose of the subject.

15. A method of assisting in the reduction of the desire of a subject to smoke tobacco comprising administering a nicotine-containing spray in accordance with any one of claims 7 to 8 to the nose of the subject in an amount which delivers a nicotine dose in the range of about 1 to about 3 mg.

16. A method of providing to a smoker a substitute for tobacco smoking comprising administering an effective dose of a composition in accordance with any one of claims 1 to 6 to the nose of the subject.

17. A method of providing to a smoker a substitute for tobacco smoking comprising administering a composition in accordance with any one of claims 1 to 6 to the nose of the subject in an amount which delivers a nicotine dose in the range of about 1 to about 3 mg.

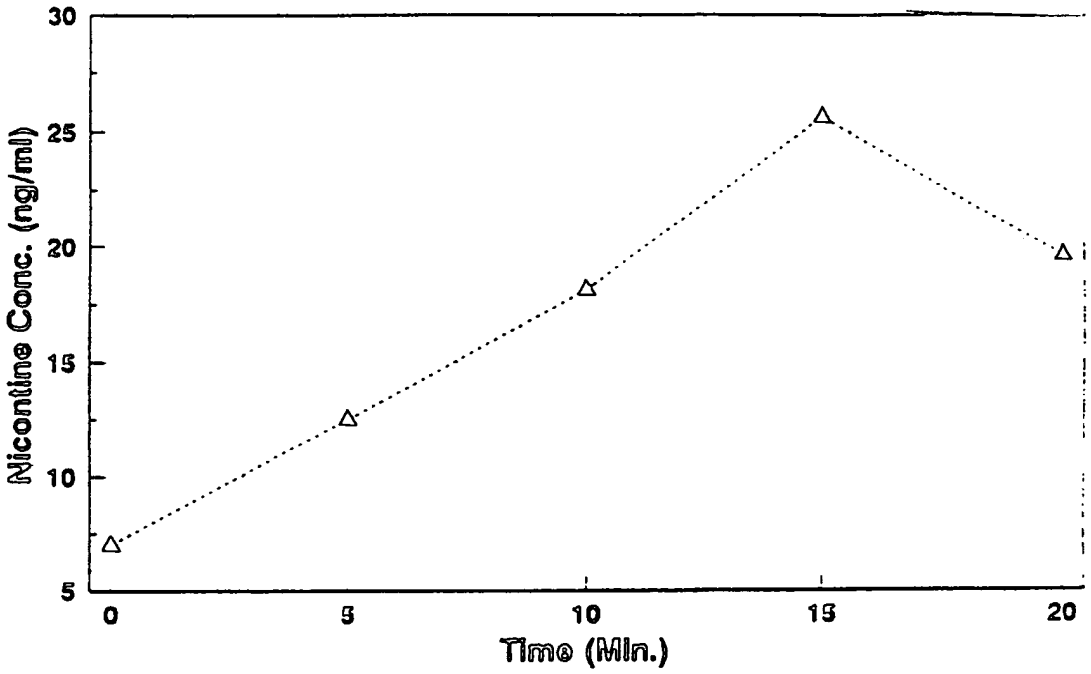
18. A method of providing to a smoker a substitute for tobacco smoking comprising administering an effective does of a nicotine-containing spray in accordance with any one of claims 7 to 8 to the nose of the subject.

19. A method of providing to a smoker a substitute for tobacco smoking comprising administering a nicotine-containing spray in accordance with any one of claims 7 to 8 to the nose of the subject in an amount which

delivers a nicotine dose in the range of about 1 to about 3 mg.

20. A composition in accordance with any one of claims 1 to 6 further comprising one or more agents selected from the group consisting of a flavouring agent, a preserving agent and an antioxidant.

FIGURE 1



INTERNATIONAL SEARCH REPORT

International Application No PCT/CA 93/00003

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K9/00; A61K31/465

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
Y	GB,A,2 133 691 (AKTIEBOLAGET) 1 August 1984 cited in the application see the whole document ---	1-20
Y	US,A,4 920 989 (J.E.ROSE) 1 May 1990 cited in the application see claims see column 5, line 51 - line 69 see column 8, line 20 - line 50 see column 9, line 49 - line 58 ---	1-20
Y	US,A,4 953 572 (J.E.ROSE) 4 September 1990 cited in the application see claims --- -/--	1-20

° Special categories of cited documents : [10]

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IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
19 APRIL 1993	12.05.93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	SCARPONI U.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	DE,A,3 241 437 (F.SCHMIDT) 10 May 1984 see claims see page 7, line 5 - line 25	1-20
Y	GB,A,2 030 862 (A.A.SMITH) 16 April 1980 see claims see page 4, line 3 - line 8	1-20
Y	DATABASE WPIL Week 8414, Derwent Publications Ltd., London, GB; AN 84-086173 (14) see abstract & RESEARCH DISCLOSURE 10 March 1984, page 239015 ANONYMOUS	1-20

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

CA 9300003
SA 68996

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 19/04/93
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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2133691	01-08-84	CA-A- 1217317	03-02-87
		CH-A- 663154	30-11-87
		DE-A,C 3401763	26-07-84
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		US-A- 5016652	21-05-91
DE-A-3241437	10-05-84	None	
GB-A-2030862	16-04-80	None	

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